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Advanced glycation end products of dietary origin and their association with inflammation in diabetes – A minireview

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Advanced glycation end products (AGEs) are a diverse group of compounds that are formed as a result of the non-enzymatic reaction between a reducing sugar such as glucose and the free NH2 groups of an amino acid in a protein or other biomolecule. The chemical reaction, by which these products are generated, is known as the Maillard reaction and occurs as a part of the body's normal metabolism. Such a reaction is enhanced during diabetes due to hyperglycemia, but it can also occur during the preparation, processing, and preservation of certain foods. Therefore, AGEs can also be obtained from the diet (d-AGE) and contribute to an increase of the total serum pool of these compounds. They have been implicated in a wide variety of pathological processes, mainly because of their ability to induce inflammatory responses and oxidative stress increase. They are extensively accumulated as a part of the normal aging, especially in tissues rich in long half-life proteins, which can compromise the physiology of these tissues. d-AGEs are abundant in diets rich in processed fats and sugars. This review is addressed to the current knowledge on these products and their impact on the immunomodulation of various mechanisms that may contribute to exacerbation of the diabetes pathophysiology.

Key words: advanced glycation end products, RAGE, inflammation, diet, diabetes

Advanced glycation end products (AGEs) are compounds derived from the non-enzymatic reaction that occurs between reducing sugars such as glucose and fructose with the amino groups of proteins, nucleic acids, and other macromolecules (Twarda-Clapa et al. 2022). On the basis of differences in their origins, AGEs are mainly classified into two types: those of the endogenous origin, which are produced naturally in the body as part of normal metabolism and whose production is exacerbated during diabetes due to hyperglycemia and those of the dietary origin (d-AGEs) produced during cooking and processing of certain foods (Liang et al. 2020).

AGEs have been described to have detrimental health effects, contributing to aging and the development of chronic diseases such as a chronic kidney disease (Bettiga et al. 2019; Fotheringham et al. 2022), neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, and amyotrophic lateral sclerosis (Guilbaud et al. 2016; Chrysanthou et al. 2022), and diabetes mellitus (Gill et al. 2019), among others. All these conditions related to the activation of a chronic and low-grade inflammatory state (Van de Vyver 2023). In this regard, several studies have described that excessive production of AGEs in the body due to

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chronic hyperglycemia is associated with inflammatory processes underlying conditions such as insulin resistance (Parwani and Mandal 2020; Yu et al. 2021), atherosclerosis (Katakami 2018), and vascular complications associated with diabetes (Ruiz et al. 2020; Steenbeke et al. 2021).

The mechanisms of action by which AGEs exert their harmful effects include: a) induction of protein cross-linking, resulting in alterations in cellular structures and functions, b) activation of specific receptors, resulting in the production of inflammatory mediators and the generation of reactive oxygen species, increasing oxidative stress, and c) impairment of mitochondrial function (Peppa and Mavroeidi 2021).

Considering that the pool of AGEs accumulated in the body reflects both endogenous production and exogenous intake (Zhang et al. 2020), the study of these food-derived compounds and their contribution to the activation and maintenance of an inflammatory state during diabetes is of special interest. For this reason, the aim of this review is to update the knowledge regarding the association between d-AGEs consumption and the induction of mechanisms that contribute to increase the inflammatory state during this disease.

Methodology

A comprehensive search was conducted in the following databases: PubMed, Scopus, and Science Direct. The different sources were consulted and reviewed independently by all the authors. The terms used individually or combined for this search were the following: Diabetes, Maillard reaction, Advanced glycation end products, RAGE, Inflammation, and Diet. In order to evaluate the quality of the evidence, only original articles were accepted.

Advanced glycation end products

AGEs are part of a complex and heterogeneous group of compounds formed exogenously and/or endogenously from a variety of precursors. In recent decades, they have aroused the interest of the scientific community due to the growing evidence of their involvement in multiple pathophysiological processes, such as diabetes, cancer, cardiovascular and neurodegenerative diseases, and even SARS-CoV-2 virus infection (Salazar et al. 2021). They are compounds recognized by several cellular receptors with the ability to activate many signaling pathways related to inflammation and oxidative stress (Zeng et al. 2019).

To understand how AGEs are formed, it is necessary to understand the Maillard reaction (Maillard 1912), which is a complex of multi-step non-enzymatic reaction that initially involves a glycation process between the carbonyl groups of reducing sugars, such as glucose and fructose, and the free amino groups of amino acids (frequently lysine and arginine), lipids and nucleic acids, resulting in the formation of a Schiff's base (Li et al. 2022). This initial reaction is relatively rapid and highly reversible. Subsequently, the rearrangement of the Schiff base occurs, leading to the formation of Amadori products, which are more stable. One of the most recognized being the glycated hemoglobin (HbA1c), widely used for its determination in the laboratory to evaluate the evolution of diabetic patients, which is formed by the binding of a valine residue of one of the β chains of hemoglobin with plasma glucose (Wang and Hng 2021).

Amadori products can subsequently undergo oxidation-reduction reactions to give a rise to compounds known as dicarbonyls; such as methylglyoxal, glyoxal, and 3-deoxyglucosone (Luo et al. 2021). These dicarbonyls initiate the advanced glycation process leading to the synthesis of AGEs, among which are mainly: methylglyoxal-hydroimidazolone (MG-H1), carboxymethyl-lysine (CML), carboxyethyl-lysine (CEL), pentosidine, and pyrraline (Poulsen et al. 2013) (Figure 1).

Advanced glycation end products of dietary origin

The amount of AGEs from the diet contributes significantly to the elevation of the content of these compounds in the blood. In this regard, healthy subjects consuming diets rich in AGEs have higher circulating concentrations of them compared to those fed diets low in these compounds (Chen et al. 2018).

The d-AGEs can reach the gastrointestinal tract as free molecules, which include amino acids and small peptides with a molecular weight of less than 5 kDa or bound to high molecular weight proteins (Delgado-Andrade 2016). Those of the low molecular weight are absorbed more efficiently, most likely by a simple diffusion (Manig et al. 2022). For example, administration to adult rats of diets containing protein-bound CML led to a higher excretion rate of this compound in feces compared to administration of the simple low molecular weight form (Roncero-Ramos et al. 2013). In this order of ideas, but in relation to pentosidine, it has been shown to be better absorbed when administered in free form than when ingested bound to proteins (Forster et al. 2005).

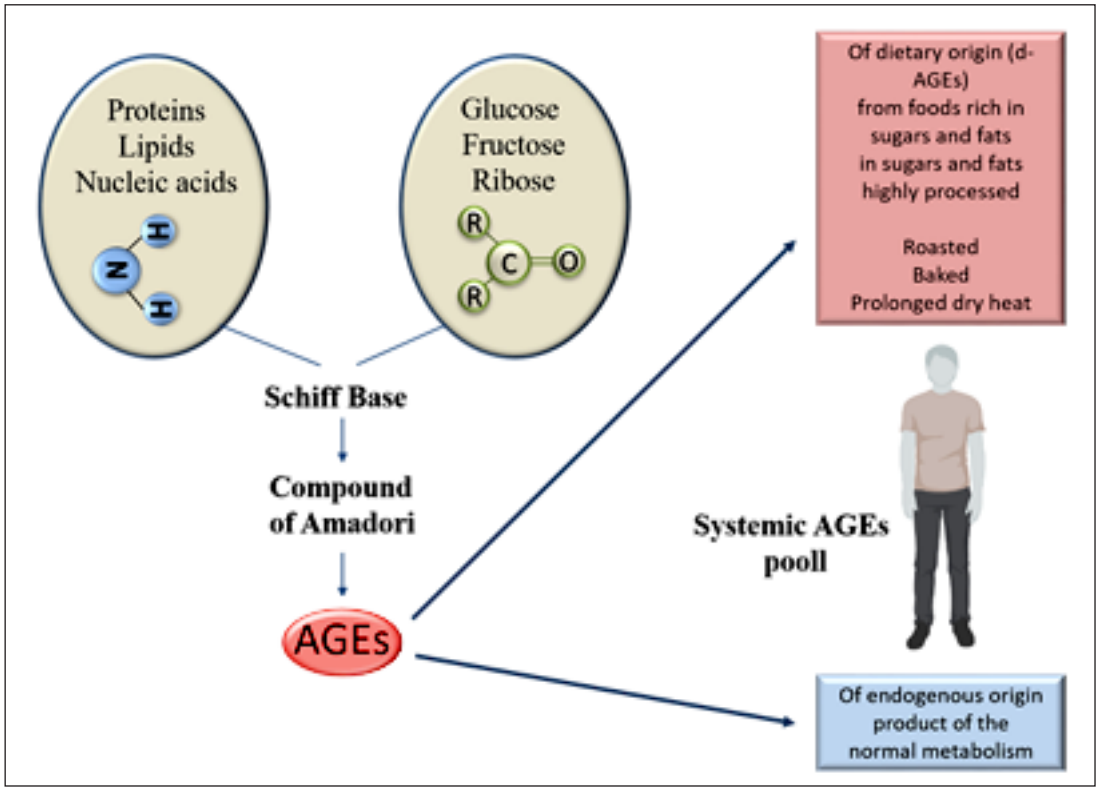


Figure 1. Simplified scheme of the formation of advanced glycation end products (AGEs) by the Maillard reaction.

The absorption and metabolism of AGEs is a complex process as the dynamics of digestion and absorption vary depending on the type of AGEs (Chen et al. 2018). After ingestion, d-AGEs are absorbed from the gastrointestinal tract and together with endogenously produced AGEs constitute the pool of circulating AGEs. However, only 10–30% of exogenous AGEs are absorbed into the systemic circulation when administered orally (Van der Lugt et al. 2020). Of these, 60% are excreted via urine (Salazar-Villanea et al. 2018). Pyrraline and pentosidine are the most absorbed d-AGEs with about 60–80 % (Munch et al. 1999). Between 20% and 50% of the ingested CML is excreted in the feces. Therefore, there is a proportion of ingested d-AGEs, which is neither absorbed nor defecated and is metabolized intraluminally by the intestinal microbiota as it has been suggested in several studies (Bui et al. 2019; Hellwig at al. 2019; Aschner et al. 2023).

The d-AGEs are formed during cooking, processing, and storage of foods as a result of the Maillard reaction, previously described and illustrated in Figure 1. Factors associated with increased formation of these compounds include: low water content during cooking, increased pH and the use of high temperatures (Gupta and Uribarri 2016; Lund and Ray 2017). Therefore, more d-AGEs are generated in foods exposed to dry heat, in processes such as grilling, frying, and baking than in foods cooked at lower temperatures for longer periods of time in the presence of higher water content, for example, boiling, steaming, stewing or simmering (Prestes Fallavena et al. 2022; Yan et al. 2023).

In the baking industry for example, the use of sodium bicarbonate increases the pH of the mixture, enhancing the formation of d-AGEs. While the addition of vinegar or lemon juice lowers the pH of the baking environment, reducing the potential for generation of these compounds (Sahi et al. 2022). On the other hand, the chemical structure of the sugars present in foods also determines the level of reactivity to the Maillard reaction. For example, the reaction is more favorable for pentose sugars, such as ribose, which react more easily than hexoses, such as glucose. In contrast, lactose, which is a disaccharide, is less reactive (Troise et al. 2020).

Foods that contribute large amounts of d-AGEs and precursors of these include: dry heat-cooked

milk powder, meats, fish, and chicken (Inan-Eroglu et al. 2020; Tristan Asensi et al. 2023); flour-based products subjected to high temperatures (bread, cookies, processed cereals) (Henle 2005); sweet sauces (Gil and Bengmark 2007), and sweet carbonated beverages containing corn syrup (Wang et al. 2017a). Alcoholic beverages and fermented foods also contain significant levels of d-AGEs because microorganisms readily produce and release these compounds (Vistoli et al. 2013).

The concentration of d-AGEs in certain foods has been determined by laboratory methods. When compounds such as CML, CEL, and MG-H1 are measured by chromatography, foods such as nuts or high-temperature processed grains and canned meats have the highest levels of d-AGEs, ranging from 2 to 5 mg for CML, 2 to 7 mg for CEL, and 15 to 60 mg for MG-H1 per 100 g of food analyzed. In contrast coffee, fruits, vegetables, butter, olive oil, and red wine contain negligible amounts of these compounds (Scheijen et al. 2016). Many of them are present in the so-called Mediterranean diet, which consists of a dietary pattern of healthy foods and is associated with a lower incidence of chronic diseases and less physical deterioration (Capurso et al. 2019).

The mediterranean diet is based on the consumption of vegetables, fruits, cereals, nuts and legumes, mostly cooked by adding substantial amounts of extra virgin olive oil, with moderate use of fish, seafood or dairy products, and limited intake of meat and alcohol (mainly red wine) (Finicelli et al. 2022).

The main compounds that may explain the health benefits of this dietary pattern are antioxidants, fiber, monounsaturated and omega-3/6/9 fatty acids, phytosterols and probiotics (Urquiaga et al. 2017). Likewise, clinical trials have confirmed the favorable influences of this diet on the risk of metabolic syndrome, obesity, type 2 diabetes mellitus, cancer, and neurodegenerative diseases (Lacatusu et al. 2019). Therefore, this diet could provide a model for the reduction of d-AGEs, with consequent reduction of their circulating levels, oxidative stress, and inflammation in patients with metabolic syndrome and diabetes (Lopez-Moreno et al. 2017).

Increased AGE affects the tissue structure and the cellular communication in diabetic patients

Elevated intake of d-AGEs has been shown to be associated in both humans and experimental models with increased oxidative stress and inflammation (Boyer et al. 2015; Guilbaud et al. 2016; Sahajpal et al. 2019; Yan et al. 2023). AGEs induce disease mainly through two general mechanisms: one direct (non-receptor-mediated) and the other indirect (receptor-mediated).

The direct mechanism involves structural modification and cross-linking of long half-life proteins such as collagen and elastin, two essential constituents of the extracellular matrix (ECM), which provides the environment for a wide variety of cells in the organism and the structural support for many tissues (Sant et al. 2020). In this context, it is important to note that cell function is profoundly affected by the environment, in which cells reside, so alterations in the ECM impact changes related to cell metabolism and function (Xing et al. 2020).

All proteins are susceptible to spontaneous reversible or irreversible non-enzymatic chemical modifications (Harmel and Fiedler 2018). In the case of the ECM, the most relevant modifications are those affecting amino acids with a high representation in collagen, such is the case of lysine and arginine, which are highly susceptible to the Maillard reaction, further predisposing collagen to undergo glycation cross-linking (Svensson et al. 2018).

When AGEs form cross-links with proteins, they interfere with the structure and normal physiological functioning of proteins. In the case of collagen, their elasticity is reduced and their stiffness is increased (Gautieri et al. 2017). Because collagen is a major component of connective tissue, it is also part of ligaments, tendons and bones. Therefore, the accumulation of AGEs leads to the weakening of their structure and certain biomechanical properties, contributing to increased skeletal fragility in diabetic patients (Stolarczyk et al. 2018). Likewise, elevated serum AGEs have been shown to limit cell proliferation and consequently delayed tendon healing (Patel and Carroll 2023). Furthermore, increased stiffness of human cartilage has been described as a consequence of cross-linking induced by AGEs accumulation, thus affecting cartilage function (Ellingson et al. 2022).

Glycated collagen is also less susceptible to degradation by metalloproteases. This interferes with the turnover of aged fibrils and, therefore, may lead to less transformation of collagen-III into collagen-I fibers, affecting the stages of wound remodeling and healing (Van Putte et al. 2016). Several research papers have described that an increase in serum AGEs levels have been associated with delayed wound healing in patients with diabetes mellitus (Qing et al. 2017). A high concentration of AGEs leads to impaired wound healing, including oxidative stress, structural and functional alterations in proteins important for wound repair, a sustained inflammatory response

through activation of transcription factors, and possible exaggerated apoptosis of cells necessary for the healing process (Wang et al. 2017b; Shaikh-Kader et al. 2019).

Cellular communication due to proteins exposed to glycation may be impaired. Key cell signaling systems are significantly altered in patients with chronic hyperglycemia. For example, in both type 1 and type 2 diabetic patients, macrovascular and microvascular complications can arise due to intracellular formation of AGEs, which induce coordinated expression of RAGE (Stefano et al. 2016; Khalid et al. 2022).

The role of AGEs in inflammation and diabetic complications

AGEs can interact with specific receptors and stimulate inflammatory responses (Rowan et al. 2018; Garay-Sevilla et al. 2020, 2021). The interaction involves the recognition of conformational epitopes on AGEs by pattern recognition receptors (PRRs) and subsequently, the delivery of biochemical signals to the nucleus in order to trigger cellular responses, such as the stimulation of inflammatory mediator synthesis (Shen et al. 2020). Different PRRs have the potential recognition capacity and binding affinity for AGEs. However, the most widely studied receptor for these compounds is the RAGE (receptor for advanced glycation end-products) receptor (Egana-Gorrono et al. 2020).

RAGE is a transmembrane protein belonging to the immunoglobulin (Igs) superfamily, due to the structural similarity of its extracellular region with these molecules (Neeper et al. 1992). The extracellular region of RAGE contains three domains including a V-type domain (variable), a C1-type domain and a C2-type domain (constant). Ligand binding to the receptor occurs through the V domain (Dong et al. 2022). The extracellular region is followed by a single transmembrane region and a short cytoplasmic region that is critical for intracellular signaling (Hudson and Lippman 2018).

Regulation of RAGE expression is encoded by the *Ager* gene, located in the Class III region of the major histocompatibility complex (Schmidt and Stern 2001). In addition to cell membrane-anchored RAGE, there are two known forms of soluble RAGE. The first type is sRAGE, which consists of extracellular ligand-binding structural domains that are proteolytically cleaved by matrix metalloproteinases, integrin α (ITGα) and metalloproteinase (ADAM)-10. The second type is endogenously secreted RAGE (esRAGE), a splice variant actively secreted by the cell. Both sRAGE and esRAGE bind to RAGE ligands, acting as inhibitors of their effects in humans (Juranek et al. 2022).

RAGE is expressed at low levels under physiological conditions, but in chronic and persistent inflammatory conditions, RAGE signaling increases and can lead to stress events that often favor mitochondrial dysfunction or cellular senescence (Zhao et al. 2018; Teissier and Boulanger 2019). Leading to the development and progression of pathological states including diabetic vascular complications, cardiovascular disease (CVD), cancer, Alzheimer's disease and a variety of pathogen-induced inflammatory diseases (Munoz et al. 2020; Pedreanez et al. 2022; Yue et al. 2022).

The hallmark of this receptor is its striking association with increased chronic inflammation. Stimulation of RAGE activates several intracellular signaling pathways, including mitogen-activated protein (MAP) kinases (ERK 1/2, p38, SAPK/JNK), STAT3, Akt and Rho GTPases (Rac1, Cdc42). These in turn activate transcription factors, NF-κB being one of the most important (Ma et al. 2023), resulting in the expression of a variety of proinflammatory genes including cell adhesion molecules, proinflammatory cytokines and other immunomodulators (Shen et al. 2020) (Figure 2).

Several studies have described that RAGE signaling and the transcription factor NF-κB activate the assembly of the NLRP3 inflammasome, a key component of the innate immune system (Son et al. 2017; Kelley et al. 2019). The NLRP3 inflammasome, is activated in response to cellular stress signals and promotes proteolytic cleavage of caspase-1, and also contributes to the secretion of proinflammatory cytokines such as IL-1β and IL-18 (Yu et al. 2018). Human research has found an association between increased NLRP3 expression and insulin resistance (Finucane et al. 2015; Rheinheimer et al. 2017). Overexpression of RAGE also promotes de novo synthesis of the p65 subunit of NF-κB which, directly induces insulin resistance by repressing transcription of the glucose transporter protein GLUT4, encoded by the Slc2a4 gene in skeletal muscles (Pinto-Junior et al. 2018; Khalid et al. 2021).

The persistence of AGEs/RAGE axis activation, NF-κB activation, and NLRP3 inflammasome activation bring about increased ROS (reactive oxygen species) production (Gasiorowski et al. 2018). Elevated ROS levels deplete antioxidant mechanisms and promote an imbalance in the intracellular redox state resulting in mitochondrial dysfunction, promoting damage to different cellular processes and

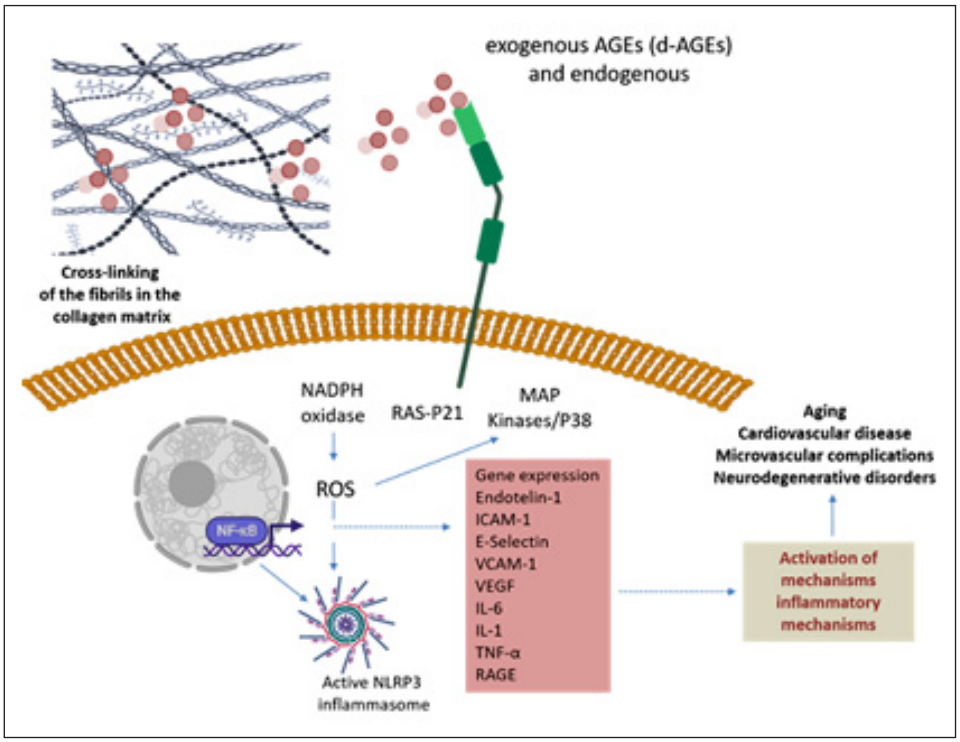


Figure 2. Proinflammatory effects of advanced glycation end products (AGEs) after binding to receptor for AGEs (RAGE). AGE/RAGE interaction on the surface of a cell leads to the initiation of a signaling cascade that leads to the activation of the transcription factor NF-κB and its translocation to the nucleus, where it enhances the transcription of target genes such as endothelin-1, ICAM-1, E-selectin, and proinflammatory cytokines. Abbreviations: ICAM-1 – intercellular adhesion molecule-1; IL-1– interleukin-1; IL-6 – interleukin-6; MAP – mitogen-activated protein kinases; NF-κB – nuclear factor kappa B; p38 – p38 mitogen-activated protein kinases; RAGE – receptor for advanced glycation end products; RAS-p21 – RAS p21 protein activator 1; ROS – reactive oxygen species; TNF-α – tumor necrosis factor-α; VCAM-1 – vascular cell adhesion molecule-1; VEGF – vascular endothelial growth factor.

cell infrastructure (Guerrero-Hernandez et al. 2014; Nowotny et al. 2015). ROS production promotes the activation of several kinases such as MAPK, ERK, IKK, p38, JNK involved in stress responses, giving rise to a vicious cycle of inflammation and ROS generation (Hurrle and Hsu 2017).

Persistent hyperglycemia during diabetes favors the increase of AGEs in the blood, which together with the d-AGEs ingested in an unhealthy diet contribute to increase the systemic pool of these compounds, favoring the activation of the AGEs/RAGE axis and the initiation of inflammatory mechanisms. At the pancreatic level, for example, they promote increased RAGE expression in beta cells (Le Bagge et al. 2020), activating an inflammatory and oxidative cascade, mitochondrial dysfunction and programmed cell death (Guan et al. 2016). AGEs-induced overexpression of RAGE in different tissues contributes to the maintenance of an inflammatory state that remains despite the fact that blood glucose levels may return to normal. This fact led researchers to coin a term known as "metabolic memory", associated with the macrovascular and microvascular complications of diabetes (Vasishta et al. 2022).

On the other hand, extracellular protein glycation contributes directly to atherosclerosis one of the main complications in diabetic patients (La Sala et al. 2019). In this regard, changes in LDL molecules prevent their uptake by receptors, which induces phagocytosis, resulting in the formation of foam cells (Ke et al. 2020). Furthermore, AGEs-induced modification of ECM proteins is one of the possible mechanisms linking d-AGEs intake to the development of atherosclerosis (Garay-Sevilla et al. 2021). Therefore, in terms of ECM modification, in addition to endogenously produced AGEs, d-AGEs

increase the overall ECM-AGEs burden, which contributes to chronic inflammation. Moreover, glycated fibrinogen is resistant to proteolysis, which promotes thrombosis and atheromatous plaque formation (Luo et al. 2019).

Additionally, oxidative stress accelerates the progression of atherosclerosis by inducing inflammation, endothelial dysfunction, thrombosis, and plaque instability (Khosravi et al. 2019). In the diabetic patients, multiple pathways induce oxidative stress, including glucose oxidation, glycation, AGEs/RAGE axis activation, and the polyol pathway (Raut and Khullar 2023).

Endothelial dysfunction and stiffening of the arterial walls place an overload on the renal microvasculature (Lentini et al. 2023). In this context, it is important to note that diabetic nephropathy is the main cause of chronic kidney disease worldwide (Gupta et al. 2023). The RAGE receptor is widely expressed in different types of renal cells: mesangial, podocytes and tubular cells (Wu et al. 2021). Thus, activation of the AGEs/RAGE axis at the renal level would contribute to the consequent inflammatory response, elevation of oxidative stress and depletion of the antioxidant mechanisms characteristic of this condition (Lentini et al. 2023).

Conclusion

AGEs are group of compounds that can be generated endogenously or incorporated as d-AGEs in the diet. The Maillard reaction, accelerated by processing and heat treatment, induces the formation of d-AGEs, particularly abundant in diets characterized by high amounts of sugars and fats, which, when ingested, contribute to increase the systemic AGEs pool. This elevation can activate inflammatory responses through the AGEs/RAGE axis and overstimulate immune cells attracted to AGEs trapped in glycated tissues and induce chronic low-grade inflammation, which underlies multiple pathological processes leading to dysfunction, persistent tissue damage and poor reconstruction after such damage.

Understanding the mechanisms involved would help to improve the diagnosis and treatment of many pathologies including diabetes, as well as to develop optimized conditions for food processing to control their ability to influence immune responses that favor the host of pathological conditions.

Conflict of Interest: *The authors reported no conflict of interest.*

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